

U.S. Application No.: 09/463,474
Attorney Docket No.: 8484-077-999

APPENDIX C
Serial No.: 09/463,474
Declaration of Dr. Hannsjörg Sinn

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Sinn *et al.*

Serial No.: 09/463,474

Group Art Unit: 1653

Filed: August 4, 2000

Examiner: D. Lukton

For: CONJUGATE FOR DIFFERENTIATING
BETWEEN HEALTHY AND
UNHEALTHY TISSUE

Attorney Docket No.: 8484-077-999

DECLARATION OF DR. HANNSJÖRG SINN UNDER 37 C.F.R. § 1.132

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, HANNSJÖRG SINN, declare and state as follows:

1. I am co-inventor of the above-identified patent application.
2. I am familiar with the Specification and claims of the above-identified patent application and the Office Actions mailed January 4, 2002 and September 12, 2002.
3. I have worked at the Deutsches Krebsforschungszentrum (German Cancer Research Center, "D.K.F.Z.") since 1968. From 1956 to 1962 I studied chemistry at the Albert Ludwigs Universität, Freiburg, Germany. In 1966 I was awarded doctor's degree (Ph.D.) at the "Technische Hochschule Darmstadt" in Darmstadt, Germany. From 1962 to 1968 I was assistant at the "Technische Hochschule Darmstadt" and was responsible for the

organization and carrying out of experimental lectures on inorganic and metalorganic chemistry. In 1968 I came to the institute of nuclear medicine at the DKFZ, Heidelberg.

4. Until 2001, I was provisional head of the department of radiochemistry and radiopharmacology of the DKFZ and involved in the development and production of radiopharmaceuticals for the *in vivo* application in the experimental and clinical nuclear medicine. Furthermore, I was involved in the development and production of macromolecular pharmaceuticals for laser induced fluorescence diagnosis (LFID) and photodynamic therapy (PDT) of solid tumors and inflammatory process. In addition, I was involved in the development and production of macromolecular conjugates for intraoperative tumor diagnosis and a new type of chemotherapy.

5. Experiments have been performed under my direction testing the ability of conjugates comprising an active substance and a native protein to treat or diagnose inflammatory or tumoral diseases.

6. In the course of such experiments, it was determined that a particular conjugate comprising a fluorescent moiety and a carrier, joined to one another via an acidic ester, an acidic amide bond or a Schiff base, selectively accumulates in cancerous or inflamed tissue.

7. A first experiment shows that tetra-(4-carboxyphenyl)porphine-HSA (TCPP-HSA) selectively accumulates in cancerous tissue. The experiment involves a C6 Glioma, implanted into rat brain. For tumor visualization the animal received TCPP-HSA. The intravenously injected dose was 1 mg/kg bodyweight (correlated to porphyrin) dissolved in

saline, administered 24 hours before brain resection. The result of the experiment is depicted in the Figure attached hereto as *Exhibit 2*. The upper part of the photograph shows a hematoxylin/eosin-stained microsection of the rat brain with the visualized tumor area in the right upper part. The lower part of the picture shows a microsection of the same area of the rat brain, irradiated with laser light (512 nm) which visualizes the TCPP. This microsection shows that only the tumor tissue takes up the TCPP-HSA.

8. In a second experiment, the selective accumulation of tetra-(4-carboxyphenyl)chlorine-HSA (TCPC-HSA) in inflamed tissue was demonstrated. The Figure depicted in *Exhibit 3* presents the accumulation of TCPC-HSA in an lymphatic node. Here, for visualization of the inflamed lymphatic node the narcotized animal received TCPC-HSA. The subcutaneously injected dose was 1 mg/kg bodyweight (correlated to the chlorine) dissolved in saline, administered two hours before the surgical intervention. The picture to the left was performed using white light; the picture to the right was at the same position using UV-light, demonstrating that the TCPC-HSA selectively accumulated in the inflamed area.

9. I further declare, under penalty of perjury under the laws of the United States of America, that all statements made herein of my own knowledge are true and that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Date

29. Jan. 2003


Dr. Hansjörg Sinn